

EPA Priorities for Biologic Markers Research in Environmental Health

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Recent advances in molecular and cellular biology allow for measurement of biologic events or substances that may provide markers of exposure, effect, or susceptibility in humans. The application of these new and emerging techniques to environmental health offers the possibility of significantly reducing the uncertainties that traditionally hamper risk assessments. The U.S. Environmental Protection Agency (EPA) health research program emphasizes the validation of appropriate biologic markers and their application to high-priority Agency issues. The rationale for EPA's biomarker research program is presented, and future research directions are discussed. Exposure biomarkers will receive most of the research emphasis in the near term, particularly body burden indicators of exposure to high-priority chemicals, such as benzene, ozone, selected heavy metals, and organophosphate pesticides. Research on effects biomarkers will attempt to validate the relationship between the observed biological effects and adverse health consequences in humans, especially for cancer, pulmonary toxicity, immunotoxicity, and reproductive/developmental toxicity.

Introduction

The United States Environmental Protection Agency (EPA) is responsible for safeguarding public health from the adverse consequences of environmental exposures. This mandate requires that EPA be both a regulatory agency and a science agency. As a regulatory agency, EPA enforces more than a dozen major environmental laws, such as the Clean Air Act and the Toxic Substances Control Act. As a science agency, EPA carries out relevant and timely research to ensure that regulatory and policy decisions are based on sound scientific information (1).

The primary goal of EPA's health research program is to reduce or eliminate critical uncertainties associated with health risk assessments for environmental exposures. To accomplish this, the EPA health research program focuses on developing an understanding of the relationships among pollutant sources, environmental exposures, and related human health effects. It spans the gamut from long-range basic research to short-term applied research and functions primarily at the interface between these two ends of the spectrum. The central position occupied by EPA's research program requires EPA scientists to be cognizant of important breakthroughs in the basic biological sciences (e.g., molecular biology, genetics, immunology) and capable of applying these scientific advances to real-world problems facing the Agency. Conversely, EPA scientists must be knowledgeable about contemporary

regulatory issues and conceptualize the basic research questions that need to be addressed (1,2).

Biologic markers provide a good example of how progress in basic research can significantly advance the state-of-the-science in an applied research area such as health risk management. The EPA relies heavily on quantitative assessment of environmental health risks as the scientific basis for decisions about how best to guard public health. By providing the methods to make biologic measurements of variations in genes, cells, and physiologic processes, the revolution in molecular biology has paved the way to measure environmental exposures more accurately and precisely, to define better associated health effects, and to improve the determination of susceptibility to pollutant exposures (3). These scientific advances will lead to better characterization of actual human health risks and a more solid scientific footing for policy and regulatory decisions.

The EPA health research program is designed to recognize the significance of these new methods, to identify those that are most relevant to the problems confronting the Agency, to encourage the development and promote the validation of suitable biologic markers, to advance the application of these techniques to environmental risk assessment, and to aid EPA decision makers in understanding and using biomarker data. The current and future importance of biologic markers for improving health risk assessments is well recognized within the Agency and has prompted state-of-the-art evaluations for the role of biologic markers in epidemiology (4), reproductive toxicology (5), pulmonary toxicology (6), and human exposure assessment (7).

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Context for Biomarkers Research

Cascade of Events from Exposure to Effect

Understanding the human health risk associated with environmental exposures involves defining the cascade of events between exposure to an environmental agent and the resulting health effect. To cause a health effect, a pollutant must be absorbed into the body, reach a target organ, and result in a biological change. For most environmental pollutants, little is known about this flow of events between exposure and health effect. Biomarkers have the potential to shed light on the factors influencing how much of a pollutant is absorbed, how much reaches a target organ, and how target dose is related to effect. Definitions of terms that are important in biomarker research are given in Table 1.

The EPA has adopted the following general definition of a biologic marker or "biomarker": a measurement of environmental pollutants or their biological consequences after the contaminants have crossed one of the body's boundaries and entered human tissues or fluids, and which serves as an indicator of exposure, effect, and/or susceptibility.

The cascade of events between exposure and environmentally induced disease is shown schematically in Figure 1. The boxes represent events that may potentially be defined, either qualitatively or quantitatively, by biomarkers.

Table 1. Key definitions for EPA's biomarker research program.

Term	Definition
Concentration	Amount of material (chemical substance) per unit of volume or mass in an environmental sample
Exposure ^a	Contact between an environmental pollutant and a living organism(s) (e.g., human, indicator organism, ecosystem); this may result from a single challenge or from contact at a given concentration over time
Absorbed dose ^a (internal dose)	Amount of material that crosses one or more of the body's boundaries; often absorbed dose is best measured by the area under the curve of intake versus time
Delivered dose ^a (target or biologically effective dose)	Amount of the absorbed dose and/or its metabolites that reaches the target (e.g., tissue, cell); often, delivered dose is best measured by the area under the curve of tissue concentration versus time
Body burden	Amount and distribution of material and/or its metabolites in the body
Biological effect	A measurable response in a molecule, cell, tissue, or fluid
Health effect	A biological effect that causes dysfunction, injury, illness, or death
Susceptibility	Increased or decreased resistance to absorption of and/or effect from chemical substances due to genetic predisposition, environmental characteristics, lifestyle factors, age, gender, or ethnicity

^aTime component may be critical.

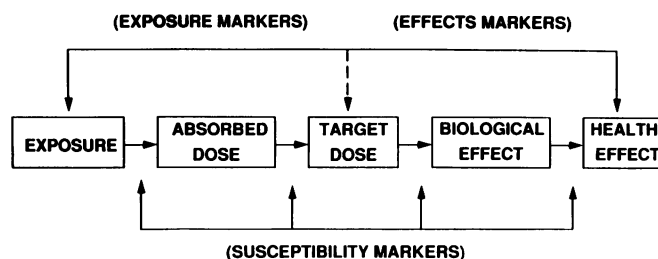


FIGURE 1. A simplified diagram of the cascade of events from exposure to health effects showing the relationships among exposure markers, effects markers, and susceptibility markers.

Exposure markers are indicators of absorbed or target dose (including an absorbed pollutant, its metabolite(s), or products resulting from interaction with endogenous substances), which are measured in a body tissue, fluid, or excreta. These biomarkers provide information concerning the chemicals to which humans are exposed. Most exposure biomarkers are indicators of absorbed dose.

Effect markers are indicators of biological response. These biomarkers provide information concerning the likely health outcomes associated with different target doses of environmental pollutants or their metabolite(s).

Susceptibility markers are indicators of whether an individual is more or less biologically susceptible to environmental health effects. Sensitive subpopulations, for example, can be pinpointed by biomarkers that measure increased absorption rate or a more severe biologic response to a given environmental exposure.

Risk Assessment Basis for Biomarkers Research

Estimating the risk associated with exposure to a given pollutant involves evaluating the likelihood and magnitude of resulting health outcomes. The EPA has adopted a formal risk assessment process, the steps of which mirror the flow of events from exposure to effect (8). These steps also identify critical questions in environmental health research: *a*) hazard identification—is the agent capable of causing an adverse effect in humans? *b*) Exposure assessment—what exposures occur or are anticipated to occur for human populations? *c*) Dose–response assessment—what is the quantitative relationship between dose and effect in humans? and *d*) Risk characterization (based on a synthesis of dose–response and exposure assessments)—what is the estimated human health risk from the anticipated environmental exposures?

Historically, exposure assessments have relied almost exclusively on measurements or model predictions of pollutant concentrations in relevant environmental media (i.e., air, water, food, soil), whereas dose–response assessments have been based primarily on animal toxicology data. In recent years, however, attention has focused on the importance of obtaining information about actual exposures experienced by humans and on the necessity of understanding the relationship between exposure and dose (pharmacokinetics) and between dose and effect (phar-

macodynamics) in human populations. It is now clear that significant improvements in health risk assessments can only be achieved by targeting research on these important issues (9).

The advent of biologic markers promises to revolutionize both exposure and effects assessments (5,6,10). As shown in Figure 1, biomarkers can provide exposure, effects, and susceptibility information based on a knowledge of the key events (e.g., absorbed dose, target dose, biological effect) that intervene between human exposures and related disease or injury. Application of exposure biomarkers to human populations will allow individuals to be classified more precisely according to exposures (e.g., high versus low exposures). Similarly, effect biomarkers will provide epidemiologists with the ability to better link human exposures with environmentally induced disease. Susceptibility markers will make it possible to more easily identify susceptible individuals and groups so that they can be considered adequately in the assessment and management of risk. Overall, biologic markers offer the possibility of using human data to make health risk assessments more meaningful, realistic, and cost effective.

EPA's Role in Biologic Markers Research

The EPA commitment to promoting the development and use of biologic markers stems from an awareness of their potential to significantly improve the accuracy of health risk assessments. From the EPA perspective, biologic marker research includes four major questions (10). *a)* Development—which actions must be taken to develop new methods and techniques for measuring biologic

markers? *b)* Validation—what scientific evidence is necessary to show conclusively that a biologic marker is an indicator of exposure, effect, or susceptibility? *c)* Application—how, when, where, and why should biologic markers be used to obtain relevant information in human populations? and *d)* Interpretation—what are the implications of biologic marker data for risk assessment, risk management, and risk communication decisions?

Together, the answers to these questions form a pathway leading to more informed decisions about the protection of public health. The respective roles of EPA scientists in addressing these questions are summarized in Table 2.

Future Research Directions

EPA scientists develop methods and make measurements aimed at constructing three types of predictive models: integrated human exposure models, physiologically based pharmacokinetic models, and biologically based dose-response models (9). Development, validation, and application of biologic markers are often an integral part of this research. The following discussion summarizes future research directions for EPA's biomarkers program.

Exposure Biomarkers

One of the major areas of concern in biomarker development is the specificity of the measurement. Current regulations to protect public health tend to be chemical specific. Therefore, biomarkers are needed to identify and characterize exposures to specific environmental pollu-

Table 2. The role of EPA scientists in the development, validation, application, and interpretation of biologic markers (10).

Activity	Definition	Role of EPA scientists
Development	Generate new methods and techniques to measure biochemical, molecular, genetic, immunologic, or physiologic indicators of exposure, effects, and susceptibility	Most development activities are conducted by organizations like NIH that perform basic biological research. Although development of biologic markers is a natural outgrowth of some EPA research, EPA scientists are primarily responsible for recognizing the potential environmental health applications of emerging technologies
Validation	Assemble adequate scientific evidence to show that the biologic marker measures what it purports to measure	A major focus of the EPA research program is establishing the validity of existing biologic markers by documenting their accuracy, precision, reproducibility, reliability, etc., in human populations
Application	Use biologic markers to measure exposure, effects, or susceptibility in human populations	The EPA research program actively promotes the application of validated biologic markers to human populations in order to improve decisions about the protection of public health
Interpretation	Risk assessment: apply biologic marker information to qualitative and quantitative evaluation of health risks from environmental exposures	EPA scientists develop risk assessment guidelines, do qualitative and quantitative health risk assessments, and identify associated research needs
	Risk management: select, implement, and enforce cost-effective risk prevention and risk reduction strategies based on consideration of risk assessment information, as well as evaluation of social, economic, and engineering issues	EPA scientists put risk assessments into perspective for decision makers, provide information on comparison of risks from various sources, and evaluate residual risks that remain after controls are implemented
	Risk communication: characterize and explain environmental health risks and actions to prevent or reduce unacceptable risks	EPA scientists participate in specifying and communicating the basis for risk assessment and risk management decisions and in explaining their impact on public health

tants. To meet Agency needs, biomarker research will emphasize two types of markers: those that are compound specific (e.g., benzene, trichloroethylene, acrylamide, styrene, nicotine, lead) and those that are indicators of relevant classes of compounds (e.g., dioxins, PCBs). The program will include three related methods development activities (7): *a*) evaluation of scientific information with regard to newly developed biomarkers and related technology, including detection methodology (i.e., can they be adapted for Agency use?); *b*) laboratory studies to ensure full characterization of potentially useful biomarkers, refinement/development of pharmacokinetic models for the analysis of biomarker data, and development of monitoring methods and devices for detecting and quantifying biomarkers, and *c*) field trials of biologic markers, methods, devices, models, and protocols.

The most promising biomarkers of exposure in the near term are body burden measurements of specific chemicals found in the blood, urine, saliva, and breath. These methods yield data directly usable in risk assessment models. Nonspecific markers of exposure, such as conjugate complexes or elevated/depressed enzyme levels, provide indirect evidence about exposure to a specific chemical or chemical mixture.

In the longer term, characterization of DNA and protein adducts (including hemoglobin, albumin, and membrane receptor proteins) to detect exposure to toxic chemicals will be emphasized. Although these measures and others, such as sister chromatid exchange (SCE), may be used as first-tier tests to suggest that exposure to a chemical has occurred, follow-up chemical-specific tests must be applied to provide data that are directly useful for exposure assessment and risk characterization.

The term "reconstructive exposure assessment" refers to the use of dose information to estimate past human exposures in a quantitative fashion. For reconstructive exposure assessment to be a practical quantitative tool, a model based on the pharmacokinetics of the particular chemical is necessary. Physiologically based pharmacokinetic models, together with measurements of the specific biomarker, form the basis to link exposure, dose, and effect. The following areas have been identified as the highest priority for future research: *a*) validate and apply biomarkers of body burden (e.g., blood and urine sampling) for field and epidemiological studies in human populations, develop pharmacokinetic models for estimating dose from tissue levels and for estimating/reconstructing external exposures from dose measures, and identify appropriate metabolites as body burden measures and *b*) refine and validate new body burden markers (e.g., receptor-xenobiotic complexes, protein adducts, and DNA adducts) for high-priority chemicals.

Effects Biomarkers

The EPA compares the benefits of reduced risk versus the costs of controls in the vast majority of its regulatory decisions. The physiological responses that serve as effect biomarkers are, however, now disease end points. Therefore, the relationship between the biomarker and the

disease must be known if biomarkers are to be directly relevant for regulatory decisions. The primary goal of EPA's effect biomarkers research will be to improve the interpretation of markers as an early indicator of an adverse health effect, with primary emphasis on cancer, pulmonary toxicity, neurotoxicity, and reproductive/developmental toxicity. Secondary emphasis will be put on immunotoxicity, heritable genetic mutations, and hepatotoxicity. For each of the critical health end points, key research needs are outlined below.

Cancer. Recent advances in cancer biology are fueling the development of more realistic cancer risk assessment models. Two of these advances are the identification of tumor growth genes (oncogenes) and tumor anti-growth genes (suppressor genes). Studies on these genes in malignant cells of certain tumor types, such as colon cancer, show that the genome of these cells contains more than one genetic change, and suggest that many mutations (perhaps 10–15) must occur before cancer results (11). Improved knowledge of the mechanism of cancer production following chemical exposure will allow the development of measures for evaluating whether humans have been exposed to carcinogens. The validation of these mechanistic studies will be an important component of EPA's biomarkers program.

Scientists currently evaluate exposure to carcinogens with DNA and protein adducts because of their chemical or chemical-class specificity. Many uncertainties exist, however, concerning the relationship of these substances to cancer, and many technical difficulties need to be resolved to expand promising detection techniques (e.g., the ^{32}P -postlabeling technique) to a wide variety of chemical classes.

Initial efforts will focus on the validation and application of DNA adducts, stressing lesion formation, rate of repair, and tissue distribution. The primary research goals will be to define the dose-response relationship between the adduct and health effect, to define the relationship between measured adduct levels and target tissue levels (when appropriate), to determine the lifetime of the adduct, to establish adduct reference standards, and to extend the methodology to a wide variety of chemical classes.

Protein adducts will also receive attention, with emphasis placed on three primary goals: to relate adducts to target site dose-response, to develop and improve methodologies and techniques (e.g., preparation and identification of adducts), and to evaluate, refine, and validate biomarkers for application to human populations (12,13).

A major aim for both DNA and protein adducts research will be to develop adducts for evaluating exposure to pollutant mixtures (including reference adduct standards) and to identify patterns or arrays of adducts characteristic of chemical classes. In addition, current techniques in molecular carcinogenesis will be applied to develop biomarkers for environmental carcinogenesis, including alterations in DNA, alterations in the expression or structure of proteins or enzymes, ultrastructural changes, growth factors, and receptors/receptor-xenobiotic complexes.

Pulmonary Toxicity. The lung is the primary route of entry for air pollutants. Most of the regulations promulgated under the Clean Air Act are based on data showing effects to the cardiopulmonary system. Because of the lung's relative accessibility, the EPA and others have used biomarkers from lung fluids and tissue to assess human exposure to air pollutants. Most of these studies have been conducted in a clinical setting, often with invasive techniques. A major goal of research on pulmonary effects biomarkers is to develop, validate, and apply less invasive markers on larger populations than is now possible (6). The focus of this work is on nasal lavage (NAL), and the goal is to improve the technique for use in clinical and field studies to obtain information about human exposures to air pollutants and resulting biologic effects. NAL values are compared to results from bronchoalveolar lavage (BAL) and parallel studies are conducted in experimental rodents to determine the linkage between biomarker measures and adverse effects.

Current efforts involve characterization of the normal parameters for the cellular and biochemical components of NAL. The purpose is to develop baseline values and to identify biomarker candidates for further characterization and validation for use in human studies. Biomarkers currently under study include: macrophage proteins, lipid

peroxidation products, DNA and protein adducts, and indicators of inflammation.

Future efforts will be designed to identify indicators of pulmonary damage in the urine of exposed individuals using techniques that are less invasive and more applicable to the general population than is NAL. Efforts will also be focused on modifying techniques developed in the biomedical community to characterize disease processes as early indicators of chronic pulmonary effects and as susceptibility markers to distinguish between responders and nonresponders. Techniques to measure these parameters will help EPA evaluate the efficacy of pollution control technologies, intervene through mitigation of exposures to individuals showing early signs of developing lung disease and to better characterize the population at risk from air pollutants. See Table 3 for a list of near and longer-term research goals.

Neurotoxicity. Many EPA regulations are based on concern over possible neurotoxicity (e.g., from organophosphate pesticides, metals in drinking water, lead in gasoline). Most measures of neurotoxicity are, however, invasive and relate only to nonreversible effects following exposure. One goal of EPA's research on biomarkers of neurotoxic effects focuses on elucidating relationships between exposure and outcome for cholinesterase and

Table 3. Future directions in effects biomarker research for selected noncancer end points.

Pulmonary toxicity	Neurotoxicity	Reproductive/developmental toxicity	Immunotoxicity
Near term	Near term	Near term	Longer term
Developing methods for assessing the functional effects of, and exposure to, acid aerosols	Determine the relationship between the cholinesterase activity in blood, peripheral nervous system, and central nervous system	Improve <i>in vitro</i> tests of sperm function (male)	Develop sensitive immunological markers (with identifiable responses at threshold levels)
Develop markers for ozone degradation products (DNA, protein products)	Determine the relationship between the degree of cholinesterase inhibition, neurotoxic esterase inhibition, and neurotoxic outcome	Improve predictive value of semen analysis; also included are efforts to improve sampling techniques, standardize results, and develop suitable sample containers (male)	Develop more quantitative markers of exposure for dose determination
Strengthen interpretation of nasal lavage (NAL) biomarkers	Determine whether age and/or species differences exist in the above relationship	Validate measurement of testosterone in saliva (male)	Improve the interpretability of biomarkers of immunotoxicity in order to predict susceptibility to disease
Longer term	Longer term	Develop methods to assess the genetic integrity of sperm (e.g., DNA damage, chromatid structure) and generalized screening methods for genetic integrity (male)	Develop and validate biomarkers that are indicators of hypersensitivity responses
Develop biomarkers for susceptibility (responders versus nonresponders)	Gel electrophoretic protein profiles from cerebrospinal fluid (CSF)	Multiple sputum samples for steroids to validate the sensitivity of the approach (female)	Improve the understanding of the mechanism(s) of chemical-induced immune alterations (i.e., immunosuppression, hypersensitivity, and autoimmunity) and identify biomarkers
Develop biomarkers as early indicators of chronic effects	Presence of nervous system-specific proteins and degradation products in CSF, plasma, and urine	Validate measurement of leutinizing hormone (ovarian cycle protocol) in mid-cycle urine (female)	
	Presence of immunoglobulins in serum directed at brain-derived antigens	Identify better markers indicative of early changes in reproductive function (male/female)	
	Presence of neurotransmitter metabolites in CSF		
	Subcellular antigens in blood and urine pointing to the extent and localization of damage to the nervous and other organ systems	Longer term	
		Develop noninvasive methods for biomarkers of preimplantation development (female)	
		Develop better markers of sperm membrane integrity <i>in vitro</i> tests of sperm function (male)	

neurotoxic esterase. Emphasis is placed on determining relationships between *a*) cholinesterase activity in blood, peripheral nervous system, and central nervous system; *b*) the degree of cholinesterase and neurotoxic esterase inhibition and neurotoxic outcome; and *c*) age or species parameters and these outcomes.

The development of minimally invasive techniques to detect nervous system-specific proteins is a key goal for future research. Studies are proceeding along four tracks: *a*) gel electrophoretic protein profiles from cerebrospinal fluid (CSF) of experimental animals are being screened; *b*) CSF from experimental animals is being searched for neurotransmitter metabolites; *c*) CSF, plasma, and urine are being screened for nervous system-specific proteins and degradation products; *d*) serum is being screened for the presence of immunoglobulins directed at brain-derived antigens.

The purpose of these efforts is to identify promising biomarker candidates and to determine which, if any, can be detected in readily accessible tissue. This is not a short-term project. It is anticipated that method development efforts will continue for the next 5–10 years before valid molecular markers for nervous system-specific proteins are developed for use in monitoring human subjects. Research goals are given in Table 3.

Reproductive/Developmental Toxicity. Humans experience a significant reproductive failure rate. Exposure to environmental chemicals has been associated with infertility, and EPA regulates a number of chemicals (e.g., dinoseb) based on their potential to cause this problem. In developing and using biomarkers to support the Agency's regulatory activities, EPA researchers will focus initially on males because of the relative ease of obtaining samples from men of reproductive age. Biomarker techniques will also be used for assessing female infertility, ability to maintain pregnancy, and heritable genetic mutations.

Initially, the highest priorities for research are to develop and validate a questionnaire and decision process for assessment of fertility problems; to develop and validate noninvasive analytical markers from urine and saliva (e.g., testosterone) that allow more frequent measures of endocrine control of reproductive function; to develop and validate biomarkers for early pregnancy that distinguish between pre- and postimplantation loss; and to improve the predictive value of semen analysis, including efforts to develop methods to assess the genetic integrity of sperm (e.g., DNA damage, chromatid structure) and generalized screening methods for genetic integrity. Efforts will also be initiated to improve sampling techniques, standardize results, and develop suitable sample containers (5). Specific goals for future research are listed in Table 3.

Immunotoxicity. Many *in vivo* and *in vitro* tests can be used to evaluate immune system responses in humans. Scientists have used these tests to demonstrate allergic reactions to environmental chemicals and altered immune function following exposure to environmental pollutants. However, because of the complexity and interactive dynamics associated with immune responses, it has been difficult to interpret these results for risk assessment. Consequently, with the exception of allergic responses,

risk assessors have had difficulty using immune system responses as a basis for regulatory decision making.

Research on immunotoxicity biomarkers is a medium priority for EPA. It will emphasize understanding the significance of immune response indicators and on using immune responses to link exposure with effects for the immune system as well as other target systems. Initial efforts will focus on developing the rat as a model system for immunotoxicology studies in order to be able to link immune parameters to other toxic end points. Normal immune parameters for cell types, immunoglobulins and cell growth factors as well as host microbial resistance parameters are being determined. In the future, animals will be challenged and screened to determine the relationships between changes in immune parameters and significant alterations in immune function. The goal is to select a subset of immune measures indicative of immune dysfunction. Emphasis will be placed on compromised resistance to microbes. A listing of future research directions is given in Table 3.

Hepatotoxicity. Research on biologic markers for liver toxicity is a medium priority for EPA. Because of the variety of serum markers for hepatic damage (14), and owing to the varying specificity and sensitivity of these markers, near-term efforts will focus on defining an optimal battery of serum biomarkers suitable for routine environmental monitoring. Efforts are also planned on serum enzyme tests and noninvasive tests for hepatic fibrosis and cirrhosis.

Other Effects. Although validation of biomarkers for other end points (e.g., renal toxicity, dermal effects) is not a priority for EPA at this time, the Agency will continue to monitor progress by others, such as the National Institutes of Health, in developing, validating, and applying relevant methodologies.

Summary

Public and private actions to protect citizens' health from the adverse effects of environmental pollutants are predicated on an established or postulated link between human exposures and resulting disease or injury. The actual health risks experienced by an individual are dependent on the seriousness of the exposure, the toxicity of the pollutant or mixture of pollutants, and his or her susceptibility to the environmental insult based on factors such as health status, diet, age, or genetic predisposition.

Biologic markers are measurements of environmental pollutants or their biological consequences after the contaminants have crossed one of the body's boundaries and entered tissues or fluids. Depending on the nature of a particular biomarker and our understanding of the cascade of events from exposure to effects, measurements may provide either qualitative or quantitative information about exposures (i.e., exposure markers), health effects (i.e., effect markers), or susceptibility (i.e., susceptibility markers).

Biologic markers promise to revolutionize the characterization of environmental health risks. By reducing critical uncertainties their application will build a stronger scien-

tific basis on which to make decisions about safeguarding public health. This, in turn, will lead to better policy and regulatory decisions and more efficacious use of scarce resources to safeguard public health.

Because the Agency is involved in all phases of the biologic marker issue, EPA scientists have identified important research questions, prioritized associated research needs, and developed a strategy to address those needs. The preceding discussion has summarized the rationale for the EPA biomarkers research program and outlined future research directions. Ultimately, the success of the program will be measured by the degree to which results improve our ability to assess the seriousness of environmental health risks.

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